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Regulation of Craving and Negative Emotion in Alcohol Use Disorder

Shosuke Suzuki¹, Maggie Mae Mell², Stephanie S. O'Malley¹, John H. Krystal¹, Alan Anticevic¹, Hedy Kober¹

¹Department of Psychiatry, Yale University School of Medicine

²Neuroscience Department, Medical University of South Carolina

Abstract

Background.—Alcohol use disorder (AUD) is a chronic, relapsing condition with poor treatment outcomes. Both alcohol craving and negative affect increase alcohol drinking, and – in healthy adults – can be attenuated using cognitive strategies, which rely on prefrontal cortex (PFC). However, AUD is associated with cognitive impairments and PFC disruptions. Thus, we tested whether individuals with AUD can successfully recruit PFC to effectively regulate craving and negative emotions, whether neural mechanisms are shared between the two types of regulation, and whether individual differences influence regulation success.

Methods.—During functional magnetic resonance imaging, participants with AUD completed the Regulation of Craving task (ROC; N=17) that compares a cue-induced craving condition to an instructed regulation condition. They also completed the Emotion Regulation task (ER; N=15) that compares a negative affect condition to an instructed regulation condition. Regulation strategies were drawn from cognitive-behavioral treatments (CBT) for AUD. Self-reported craving and negative affect were collected on each trial.

Results.—Individuals with AUD effectively regulated their craving and negative affect when instructed to do so using CBT-based strategies. Regulation was associated with recruitment of both

*To whom correspondence should be addressed, Hedy Kober, Ph.D., Yale University, Clinical & Affective Neuroscience Lab, One Church St. Suite 701, New Haven, CT 06510, hedy.kober@yale.edu.

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common and distinct PFC regions across tasks, as well as reduced activity in regions associated with craving and negative affect (e.g., ventral striatum, amygdala). Effective regulation of craving was associated with negative alcohol expectancies.

Conclusions.—Both common and distinct regulatory systems underlie regulation of craving and negative emotions in AUD, with notable individual differences. This has important implications for AUD treatment.

Keywords

Alcohol Use Disorder; fMRI; craving; negative affect; regulation of craving; emotion regulation

Introduction

Today, alcohol remains the most commonly-used psychoactive substance (other than caffeine; (1, 2)), despite mounting evidence of its harmful effects (3). Importantly, 9-17% of drinkers meet criteria for alcohol use disorder (AUD), a chronic, relapsing condition (2, 4, 5) with enormous societal costs (6). Many individuals with AUD never receive or delay treatment (7-9), and the modal treatment outcome is relapse (10, 11). Therefore, it is important to understand the factors that contribute to substance use disorders (SUDs), including AUD.

Craving and Its Regulation in AUD.

One factor that contributes to drug and alcohol use is craving, defined as “a strong desire or urge” (12). Craving has been linked to drug and alcohol use across retrospective reports (13-15), prospective clinical studies (16-21), and ecological momentary assessments (22-25). Such studies have found that craving is cross-sectionally and prospectively associated with increased drug use. Thus, craving was added as a diagnostic criterion for SUDs in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; (12)).

Importantly, craving can be triggered by stimuli that have previously been associated with the substance (26). Such *cue-induced craving* has been directly linked to drug and alcohol use (27-31). Additionally, intensity of cue-induced craving predicts relapse to drugs (20, 32) and alcohol (33-36), and increases in cue-induced responses are reported months into abstinence (37). As such, cue-induced craving contributes to high rates of relapse, and thereby to the chronicity of SUDs and difficulty of treatment.

Given the role of cue-induced craving in relapse and SUD maintenance, regulation of craving has become an important clinical target. In fact, cognitive behavioral therapies (CBTs) for SUDs focus on situations in which individuals may be exposed to drug cues, crave, or seek the substance (38). To cope with such “high-risk situations,” CBTs teach cognitive strategies, such as orienting individuals to focus on the negative consequences of drug use (vs. pleasurable consequences (38)). Importantly, recent experiments have demonstrated that cognitive strategies can reduce cue-induced craving for cigarettes (39-41), stimulants (42, 43), and food (39, 40, 44-46). Clinically, implementation of such strategies has been associated with reduced smoking (47), and acquisition of such skills mediate CBT

treatment success for drug and/or alcohol use (48). These data suggest that cognitive strategies are an active component of CBTs, at least in part due to their effects on reducing craving.

However, only one study, to our knowledge, has experimentally investigated regulation of craving in AUD (49). In this previous study, we taught participants to focus on the negative consequences of drinking during cue-induced alcohol craving (38-40). We observed that—compared to social drinkers—individuals with AUD were less able to regulate craving using this CBT-based cognitive strategy (49). This is consistent with abundant evidence linking alcohol drinking to deficits in cognitive control (for review, see (50)), and studies that further link deficits to subsequent alcohol use (e.g., (51)).

Despite the clinical importance of the ability to regulate craving, its underlying neural mechanisms have not been investigated in AUD. Using functional magnetic resonance imaging (fMRI), we previously showed that regulation of craving in cigarette smokers depends on recruitment of prefrontal brain regions, such as dorsolateral, ventrolateral, and dorsomedial prefrontal cortex (dlPFC, vlPFC, dmPFC; (40)). This was accompanied by relative deactivations in reward-related regions, including the ventral striatum and ventromedial prefrontal cortex (VS, vmPFC; (40)). Similar findings have been reported in cocaine use disorder (43) and with regulation of food craving (52-54).

Alcohol Expectancies.

Regulation strategies require individuals to focus on the negative effects of alcohol; thus, individual differences in expectancies about alcohol may affect regulation of craving. For example, individuals who drink the most report higher expectations for the positive effect of alcohol (55), and may disregard the negative consequences of excessive drinking. However, it is unknown whether individuals who have higher negative expectations are better at regulating craving. Importantly, identification of individual differences that modulate regulation processes may help optimize and individualize treatments.

Negative Affect and Its Regulation in AUD.

Negative affect is also thought to contribute to drug and alcohol use (56-58). Indeed, many theories of SUDs and AUD focus on reduction of negative affect as motives for consumption (57, 59-61). In turn, the reduction of negative affect is considered negatively reinforcing, increasing the likelihood of continued use (62). Consistently, several lines of work link negative affect, drug use, and SUDs. First, SUDs (including AUD) frequently co-occur with mood and anxiety disorders (6, 56, 63-65), and major depression predicts AUD (66). Second, levels of self-reported negative affect have been linked to drug use. For example, negative affect predicts relapse in cigarette smokers (16) and correlates with drinking problems in adult drinkers (67). Third, negative affective states trigger craving across drug types. Specifically, acute induction of negative affect has been shown to increase craving for cigarettes (68), cocaine (69), opiates (70), and alcohol (33, 71, 72). Fourth, negative affect and stress have been directly linked to drug use and relapse after treatment (72).

Given the relationship between negative affect and drug use, regulation of negative affect has important implications for SUD treatment (along with regulation of craving; (56)). A rich

literature has demonstrated that healthy adults can use cognitive strategies to regulate affective responses to aversive stimuli (73). A recent meta-analysis demonstrated that regulation is associated with recruitment of dlPFC, vlPFC, and dmPFC (similar to regulation of craving), and with reduced activation in amygdala (74). However, cognitive emotion regulation has been poorly investigated in SUDs, with only two published studies to date (to our knowledge). In these studies, cognitive strategies reduced negative emotional responses towards negative images in nicotine-dependent cigarette smokers (75) and cocaine use disorder (76).

Shared Neural Systems Supporting Regulation of Craving and Negative Emotion.

An important remaining question is whether shared neural mechanisms underlie the implementation of cognitive strategies to regulate craving and negative affect. Prior studies suggest that neural activation during different types of self-control may converge in PFC (77, 78). One study in cigarette smokers found that dlPFC, vlPFC, and dmPFC/pre-supplementary motor area (preSMA) were activated across self-control of emotion, craving, and motor impulses (78), suggesting a common prefrontal pathway supporting various forms of cognitive regulation. However, this has yet to be replicated in any population, and has not been investigated in AUD. Importantly, this question has implications for whether regulation success in one domain may generalize to other domains of regulation.

Notably, AUD has consistently been linked to disruptions in PFC function and structure (for review, see (79)). Human imaging studies have documented reduced prefrontal grey matter volume in AUD (80-82), which was further associated with executive function impairments (80). In addition, alcohol drinkers exhibit altered PFC activity, including hyperactivity in vmPFC and anterior cingulate cortex (ACC) during relaxing imagery (71), hypoactivity in mPFC and ACC during threat processing (83), and disruptions in PFC during negative emotional processing (84-86). Investigating whether individuals with AUD can effectively recruit PFC mechanisms during regulation will inform treatment approaches that utilize cognitive strategies (48).

The Current Study.

To address these questions, we used fMRI to scan individuals with AUD while they completed the Regulation of Craving (ROC) and Emotion Regulation (ER) tasks. These tasks are specifically designed to examine the neural mechanisms underlying cognitive regulation of craving and negative affect – invoked using alcohol-related and negatively-valenced pictures, respectively – given the importance of these processes to AUD. In addition, we tested whether there are shared prefrontal mechanisms across these forms of cognitive regulation. Further, we used self-report to assess regulation success across tasks, and whether regulation success for alcohol craving is modulated by individual differences in negative alcohol expectancies.

Methods and Materials

Participants.

Twenty-six individuals with AUD participated in this two-visit outpatient study. Recruitment was conducted via advertisements in the New Haven community. Participants were eligible if they: 1) Met diagnostic criteria for alcohol abuse or dependence (assessed via the Structured Clinical Interview for Diagnosis for DSM-IV); 2) Did not meet criteria for any other Axis I disorder, except nicotine dependence; 3) Consumed 25 drinks/week for men and 20 drinks/week for women; 4) Consumed alcohol on 4 days/week; and 5) Could understand and consent to study procedures. Participants were excluded if they: 1) Had contraindications for MRI (e.g., pregnancy, metallic implants); 2) Reported currently taking centrally-active medications; 3) Tested positive for psychoactive drugs (cocaine, opiates, methamphetamine, amphetamine, PCP, or benzodiazepines) as indicated by urinalysis; or 4) Provided false information during screening. All participants provided informed consent during the initial screening visit and returned for fMRI scanning at Yale University's Magnetic Resonance Research Center.

A priori sample size and data-collection stopping targets were based on sample and effect sizes reported at the time in the extant emotion regulation literature (i.e., commonly around 16-20 participants; for a meta-analysis, see (74)), on our prior study with the ROC task (N=21; (40)), and on availability of funding. Four participants could not complete the MRI session due to unanticipated claustrophobia. One participant provided false information during screening, which was discovered following completion of the study; their data were removed prior to analysis (specifically, we discovered that the participant was previously enrolled in another study in our lab and had provided conflicting information regarding their substance use). Data from another participant were excluded due to non-compliance (e.g., no responses in some runs). All but the first two participants were scanned in the afternoon (~4pm) to minimize any diurnal variations in alcohol craving; therefore, the two participants scanned in the morning were excluded from ROC analysis. In addition, ROC data from one participant and ER data from three participants were excluded for excessive motion or technical errors. Thus, the final sample included 17 participants for the ROC task and 15 participants for the ER task. All procedures were approved by Yale University's Institutional Review Board.

Procedures.

Participants were instructed to abstain from alcohol on scanning day, and from eating for 2 hours prior to their visit. Alcohol abstinence was confirmed using a breathalyzer (BACtrack, San Francisco, CA). Psychoactive substance use was tested via urinalysis (Redwood Toxicology Laboratory, Santa Rosa, CA).

Negative Alcohol Expectancy Questionnaire.

The Negative Alcohol Expectancy Questionnaire (NAEQ; (87)) assessed participants' expectations about the negative consequences of alcohol (three subscales: Same-day, Next-day, Long-term). The long-term subscale is known to predict abstinence 3 months later (88).

Regulation of Craving (ROC) Task.

The ROC task assesses craving and regulation of craving (39, 40, 42, 45, 49, 89) using an event-related design. On each trial, participants were presented with a unique picture of alcohol or food shown to induce craving in prior studies (Figure 1A; (39, 40, 49)). Prior to the picture, an instruction cue appeared in the center of the screen, orienting participants to view the picture in one of two ways: (1) Craving condition: “think about the immediate effects of consuming the item,” indicated by the word NOW, or (2) Regulation condition (based on CBT): “think about the long-term effects of regularly consuming the item,” indicated by the word LATER. Importantly, to minimize demand characteristics, participants were not explicitly told to reduce craving. Then, following an exponentially-jittered interstimulus interval (ISI= \sim 2.73s; (90)), participants rated the intensity of their craving on a scale from 1 (not at all) to 5 (very much). Trials were separated by exponentially-jittered intertrial intervals (ITI= \sim 3.43s; (90)). Participants completed 4 runs (20 trials/run).

Emotion Regulation (ER) Task.

The ER task assesses the regulation of negative affect (73, 74, 91, 92) in response to negative images using an event-related design. On each trial, participants were shown an instruction cue orienting them to view a subsequent picture in one of two ways: (1) Look condition: “simply look at the picture,” indicated by the word LOOK, for neutral and negative pictures, or (2) Regulation condition: “think about the image in a less negative way,” indicated by the word REAPPRAISE, for negative pictures only (Figure 1B). Unique negative and neutral pictures were drawn from the International Affective Pictures System (93). Following exponentially-jittered ISIs (\sim 2.8s; (90)), participants rated the intensity of their negative affect on a scale from 1 (not at all) to 5 (very negative). Trials were separated by exponentially-jittered ITIs (\sim 3.5s; (90)). Participants completed 4 runs (15 trials/run).

Behavioral Data Acquisition & Analysis.

The tasks were programmed in E-Prime version 2.0 (Psychology Software Tools, Sharpsburg, PA), and presented using a back-projection mirror. Participants provided ratings using an MRI-compatible 5-button box. Order of tasks was counterbalanced. Analyses of behavioral data were conducted in SPSS (IBM, Armonk, NY). For the ROC task, we conducted a 2 Instruction (NOW/LATER) \times 2 Image Type (alcohol/food) repeated-measures ANOVA. For the ER task, we conducted a one-way ANOVA with Condition as a within-subjects factor with 3 levels (REAPPRAISE-Negative/LOOK-Negative/LOOK-Neutral). Significant effects were followed-up using post-hoc pairwise comparisons. Finally, following prior studies using the ROC and ER tasks (e.g., 40, 49, 89, 92, 94), we calculated a “regulation success” score for each participant, for each task. Specifically, for the ROC task, the mean self-reported craving during the regulation condition was subtracted from that during the craving condition, and for the ER task, the mean self-reported negative affect during the REAPPRAISE-Negative condition was subtracted from that during the LOOK-Negative condition. Thus, for each task, positive regulation success scores indicated successful reduction in craving or negative affect, whereas negative scores indicated an increase in craving or negative affect during the regulation condition. We then assessed whether negative alcohol expectancies correlated with regulation success in the ROC task,

and whether ROC regulation success correlated with regulation success in the ER task. A missing value on the NAEQ was imputed for one participant (95, 96). An alpha level of $p < 0.05$ was used across analyses.

fMRI Data Acquisition & Analysis.

Participants were scanned in a 3-Tesla Siemens TIM-Trio scanner (Siemens AG, Munich, Germany). One participant was scanned in a 3-Tesla Siemens Prisma due to scanner upgrade during the study period (between-scanner differences are minimal, and do not compare to physiological noise (97)). Importantly, excluding this participant did not change the main findings; thus, we included their data in analyses. Scan parameters followed Human Connectome Project recommendations (98). Functional images were acquired with T2*-weighted echo-planar pulse sequences with a multiband acceleration factor of 6 (TR/TE=700/31ms; flip angle=55°; FoV=210×210mm; 54×2.50mm slices). High-resolution structural images were acquired using a single-shot, magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR/TE=2400/2.01ms; flip angle=8°; FoV=256×256mm; 224×0.80mm slices).

Functional images were preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) following our prior work (e.g., (99)). Specifically, functional images were co-registered to the structural image, motion-corrected, warped to the Montreal Neurological Institute template, and smoothed using a Gaussian filter (5mm full-width half-maximum). Both before and after preprocessing, data were subjected to multiple tests for quality assurance, and inspected for signal spiking and motion. Volumes were discarded if the root mean square of motion parameters exceeded half of a single voxel size (100). First-level modeling of trial events was conducted using robust regression to reduce the influence of strong outliers (99, 101, 102). Following prior work (e.g., (40, 92)), for both tasks, the instruction cue and picture presentation periods were modeled together as box-car regressors convolved with the hemodynamic response function, using the general linear model. The rating period, motion parameters, their squares, and high-pass filter parameters were included as additional regressors of no interest. Second-level contrasts identified regions that were differentially activated between conditions. Specifically, we calculated the [LATER>NOW] contrast for the ROC task, and [REAPPRAISE-Negative>LOOK-Negative] for the ER task. Additionally, parametric analyses were performed to identify regions that covaried trial-by-trial with self-reported levels of craving in the ROC task, and negative affect in the ER task.

To identify regions that were mutually activated during regulation across tasks, we performed a formal conjunction analysis between the primary group contrasts from the two tasks using the minimum statistic approach, as previously described (103, 104), and as we implemented previously (99, 101). The conjunction map was defined by setting the statistical value at each voxel to the smaller of the two contrasts ([LATER>NOW] for ROC & [REAPPRAISE-Negative>LOOK-Negative] for ER). This allowed us to formally represent voxels that were statistically significant across both contrasts. Finally, to test whether the regions identified in the conjunction overlapped with those previously reported as commonly-activated across self-control types in smokers, we masked the conjunction

results with 6mm spheres centered around these peaks (78): vIPFC (−48, 20, −6), dlPFC (−44, 24, 30), and dmPFC/preSMA (−4, 16, 52).

Results were familywise-error corrected at a combined voxel-wise and cluster threshold (k) of $p < .05$, with a voxel-wise threshold $p < .001$ (105); see Supplemental Information for analyses corrected with $p < .005$ voxel-wise threshold). The estimated spatial smoothness of the residual was used to determine the k threshold for each second-level map: ROC LATER>NOW ($k=27$), ROC effect of craving as parametric regressor ($k=56$), ER REAPPRAISE-NEGATIVE>LOOK-Negative ($k=27$), ER effect of negative affect as parametric regressor ($k=68$), and ROC & ER conjunction map ($k=2$). VS/sgACC and vmPFC/OFC in the ROC task and amygdala in the ER task were selected as *a priori* regions of interest (ROIs), given evidence implicating these areas in craving and affective processing, respectively. To do this, the amygdala ROI was defined using an anatomical mask, while the VS/sgACC and vmPFC/OFC ROIs were defined using spherical ROIs ($r=6\text{mm}$) centered around peaks previously observed during regulation of craving in cigarette smokers (VS/sgACC: −3, 11, −2; vmPFC/OFC: 0, 56, −2; (40)). These regions were considered significant at a familywise-error rate of $p < .05$ using a voxel-wise threshold of $p < .005$ and small-volume correction (SVC).

Results

Self-Reported Craving in the ROC Task.

We found a main effect of Instruction ($F_{(1,16)}=13.04$, $p=.002$) such that participants reported lower craving in LATER than NOW, as expected ($t_{(16)}=-3.58$, $p=.003$; Figure 2A; Figure S1). We also found a main effect of Image Type ($F_{(1,16)}=5.50$, $p=.03$) such that alcohol images induced significantly greater craving than food ($t_{(16)}=2.48$, $p=.02$). We did not find a significant interaction ($p=.24$). Regulation success did not significantly differ between image types ($p=.24$).

Self-Reported Negative Affect in the ER Task.

We found a main effect of Condition ($F_{(1,14)}=57.70$, $p<.001$), such that participants reported greater negative affect when looking at negative images than neutral images ($t_{(14)}=10.59$, $p<.001$), and reported lower negative affect when instructed to reappraise negative images compared to looking at them ($t_{(14)}=-3.40$, $p=.004$), consistent with prior work (Figure 2B; Figure S1). Regulation success in the ER and ROC tasks were not significantly correlated ($p=.41$).

Correlation with Negative Alcohol Expectancy.

Regulation success during alcohol trials of the ROC task was significantly and positively correlated with long-term negative alcohol expectancies ($r_{(15)}=0.54$, $p=.03$), such that participants with greater expectancies about the long-term negative effects of alcohol were better able to regulate their craving. Regulation success did not correlate significantly with same-day or next-day subscales ($p>.12$).

Neural Activity during Regulation of Craving.

We observed greater recruitment of dlPFC and vlPFC during cognitive regulation of craving ([LATER>NOW]; Figure 3A, Table 2A). We also observed relative deactivations in VS/sgACC and vmPFC/OFC (*a priori* ROIs). We did not find significant modulation of activity in the amygdala.

Neural Activity during Emotion Regulation.

We observed increased activations in dlPFC, vlPFC, and dmPFC during emotion regulation ([REAPPRAISE-Negative>LOOK-Negative]; Figure 3B, Table 2B). We also observed a relative deactivation in the amygdala (*a priori* ROI). We did not find significant modulation of activity in VS/sgACC or vmPFC/OFC.

Parametric Modulation.

We observed a significant positive association between trial-by-trial brain activity and craving in vmPFC/OFC and VS/sgACC (Figure 4; Table 2C). We did not observe any parametric associations between brain activity and negative affect during the ER task.

Conjunction between Regulation of Craving and Emotion.

We observed significant co-activation in left vlPFC between regulation of craving (ROC: [LATER>NOW]) and negative affect (ER: [REAPPRAISE-Negative>LOOK-Negative]; Figure 5; Table 2D; See Supplemental Information for dlPFC in analysis using a $p < .005$ threshold). As a result, this analysis revealed that subregions of the right dlPFC and left vlPFC were uniquely active during regulation of craving, but not emotion regulation (Table 2). When the conjunction analysis was masked with regions previously observed in smokers during various forms of cognitive control, we observed significant overlap in left vlPFC.

Discussion

The results indicate that individuals with AUD can regulate craving as well as negative affect using cognitive strategies. Further, those who reported greater long-term negative alcohol expectancies were more successful at regulating their craving. Importantly, regulation was accompanied by increased activity in dlPFC, vlPFC, and dmPFC, and relative deactivations in regulation targets, namely the VS/sgACC and vmPFC/OFC for craving and the amygdala for negative affect. Furthermore, VS/sgACC and mPFC/mOFC activity parametrically varied with moment-to-moment craving. Finally, formal conjunction analysis showed that activations during both types of regulation spatially converged in vlPFC (and dlPFC at a more relaxed threshold; See Supplemental Information). These findings have important implications for our understanding of AUD, CBT, and SUD treatment more broadly.

Our results demonstrate that individuals with AUD can use cognitive strategies to reduce cue-induced craving for both alcohol and food, consistent with our prior behavioral findings (49). This is an important replication given the wealth of research linking alcohol use and AUD to cognitive impairments (106). In addition, we provide novel evidence suggesting that individuals with AUD can successfully regulate negative affective responses towards

negative stimuli. As such, these findings provide experimental validation of cognitive strategies that are used in psychological AUD treatments.

Interestingly, although results suggest that individuals with AUD are *able to* use cognitive strategies to regulate craving and negative emotion in a laboratory setting, they *may not spontaneously do so* in everyday life. Indeed, AUD is clinically characterized by impaired control of emotion (12, 56). This seeming contradiction – whereby individuals with AUD can use regulatory strategies in the lab despite apparent deficits in everyday life – parallels findings in depression. Specifically, studies have demonstrated that individuals with depression can use cognitive reappraisal to reduce negative affect in laboratory studies (e.g., (107, 108)); nevertheless, they are also less likely to spontaneously do so (109, 110). This may also be true for individuals with AUD who are able to regulate craving, but may not do so in everyday life. Thus, the underlying problem may not be in capability, but rather in a more downstream process that negatively affects the tendency to execute regulation strategies. Alternatively, individuals with AUD may not regulate their craving in everyday life simply because it is more difficult to do so, relative to the laboratory setting. In either case, the findings suggest that targeted training in regulation of craving and negative emotion might be helpful for this population, to enhance individuals' ability to regulate even in difficult moments and to make strategies more accessible. This could increase the likelihood of regulation in everyday life (89, 111, 112).

Notably, successful regulation of alcohol craving was associated with long-term negative expectancies about alcohol. This finding suggests that the current strategy – namely, thinking about the long-term negative effects of alcohol – may work best in individuals who already have negative expectancies. This is consistent with prior reports that negative alcohol expectancies are associated with abstinence motivation prior to alcohol treatment (113), and predict subsequent abstinence (88). Thus, one intriguing possibility is that negative expectancies influence treatment outcome via their effect on regulation of craving. Alternatively, negative expectancies may represent individuals' motivation for change (7-9). Both accounts point to enhancing negative expectancies as an important target of treatment.

Neuroimaging analyses revealed that, during cognitive regulation of craving and negative emotion, individuals with AUD recruit prefrontal regions, including dlPFC, vlPFC, and dmPFC. These results echo findings from prior imaging work on emotion regulation in healthy adults (74, 114) and regulation of craving in cigarette smokers (26) and cocaine users (43). However, to our knowledge, this is the first study to examine the neural mechanisms underlying these cognitive regulation strategies in AUD. Moreover, the current findings are somewhat surprising given consistent reports of disruptions in prefrontal function and structure in AUD (e.g., 80, 81, 82).

Importantly, along with PFC recruitment, we observed relative deactivations in the VS/sgACC and vmPFC/OFC during regulation of craving. Parametric modeling demonstrated that VS/sgACC and mPFC/OFC activity tracked with moment-to-moment changes in craving across image types and instructions. These results are consistent with meta-analyses showing that craving for drugs and food is associated with VS/sgACC and mPFC/OFC activations (115-118), and with the broader role proposed for these regions in value

computation (119-122). Taken together, these results provide further evidence for the role of a prefrontal-striatal pathway in the regulation of craving (40).

Across both tasks, conjunction revealed co-activation of vIPFC during regulation (and dlPFC at a more relaxed threshold; See Supplemental Information). Interestingly, this region overlapped with a region previously identified across three domains of cognitive control in cigarette smokers (78). We also observed non-overlapping activations in PFC subregions during regulation of craving and negative emotion. These spatial differences may be partially attributable to differences in strategy implementation between the ROC and ER tasks: The strategy used for alcohol cues involved focusing on the negative consequences of consumption, whereas the strategy used for negative stimuli involved generating positive re-interpretations. Thus, differential engagement of prefrontal regions associated with autobiographical memory (e.g., (123)), prospective thinking (e.g., (124)), self-referential processing (e.g., (125)), and affective processing (e.g., (126)) is likely.

In addition, given that domain-specific subcortical targets were modulated during regulation of craving and negative emotion, different cortical mechanisms may be engaged during each type of regulation, forming distinct regulatory pathways. That is, although PFC activation during both types of regulation largely overlap, different cortical circuits are likely engaged in the modulation of distinct subcortical targets. Importantly, these neural differences may account for the absence of correlation between regulation success for craving and regulation success for negative emotion. In other words, behavioral differences between the two tasks may be due to the domain-specificity of pathways that underlie these two types of regulation.

Importantly, the sample size was relatively small. Although this is often the case with fMRI studies in AUD (127-130) and in clinical populations more generally (for meta-analysis, see (131)), this is a limitation that reduces the likelihood of detecting small effects and may limit generalizability of the findings. We hope that future studies will expand upon this work with larger samples. Such studies could also include healthy controls and social drinkers to examine whether regulation success relates to drinking severity. Such studies could also test whether AUD affects prefrontal-subcortical pathways within and across domains of regulation (e.g., selecting appropriate regulatory outputs). Additionally, longitudinal designs could test the relationships between negative alcohol expectancy, regulation of craving, and clinical outcomes. Finally, given that AUD individuals are capable of regulating craving when instructed to do so, the next important step may be to identify ways to train them to increase their tendency to use such strategies in their daily lives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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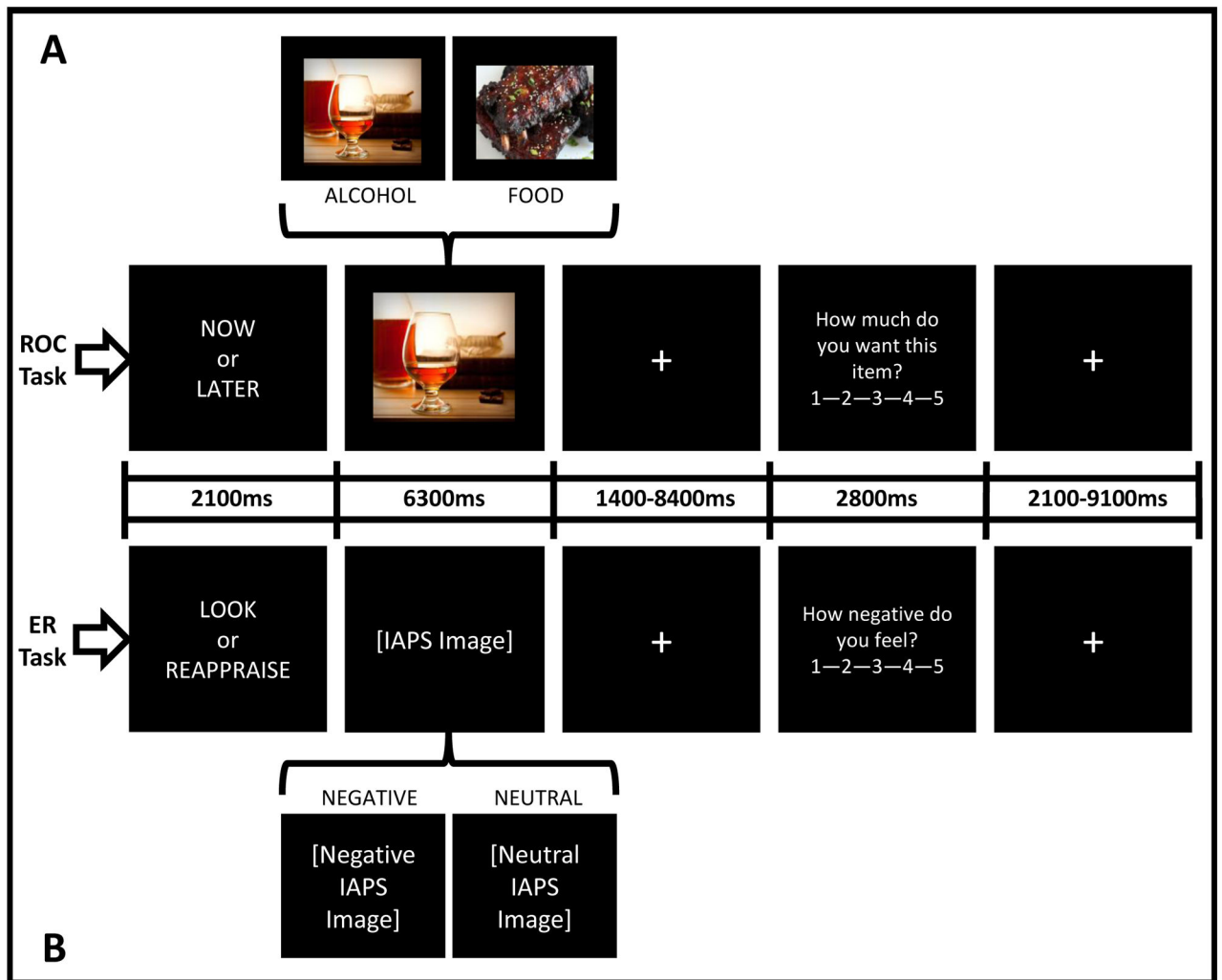


Figure 1.

Schematic representation of a single trial of (A) the Regulation of Craving (ROC) and (B) the Emotion Regulation (ER) tasks. Trials in the two tasks followed a parallel structure: Each trial started with an instruction presented in the center of the screen (NOW or LATER in ROC; LOOK or REAPPRAISE in ER) for 2100ms. The instructions oriented participants to focus on the subsequently-presented picture in particular ways. Then, a picture was presented for 6300ms (alcohol or food in ROC; negative or neutral in ER). A jittered inter-stimuli interval (1400-8400ms) followed the image presentation. Participants were then asked to make a rating of their craving (ROC) or negative affect (ER) on a 5-point scale (2800ms). The inter-trial interval was jittered 2100-9100ms.

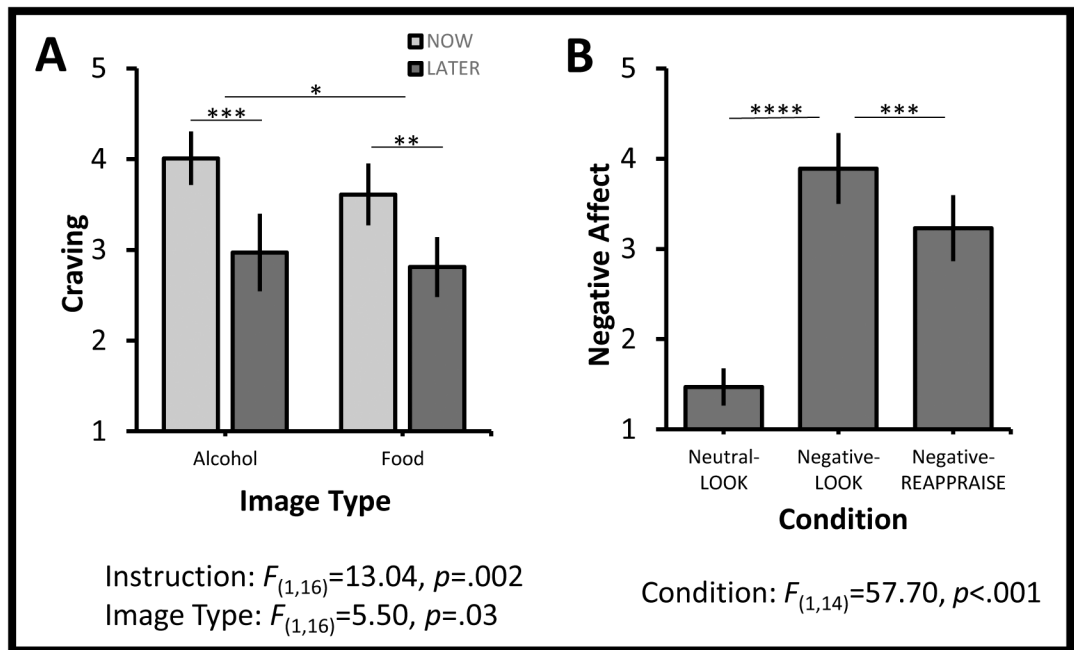


Figure 2. Behavioral ratings (y-axis) from the (A) Regulation of Craving (ROC) and (B) Emotion Regulation (ER) tasks, separated by condition (x-axis). Significance is noted: * $p<.05$, ** $p<.01$, *** $p<.005$, and **** $p<.001$.

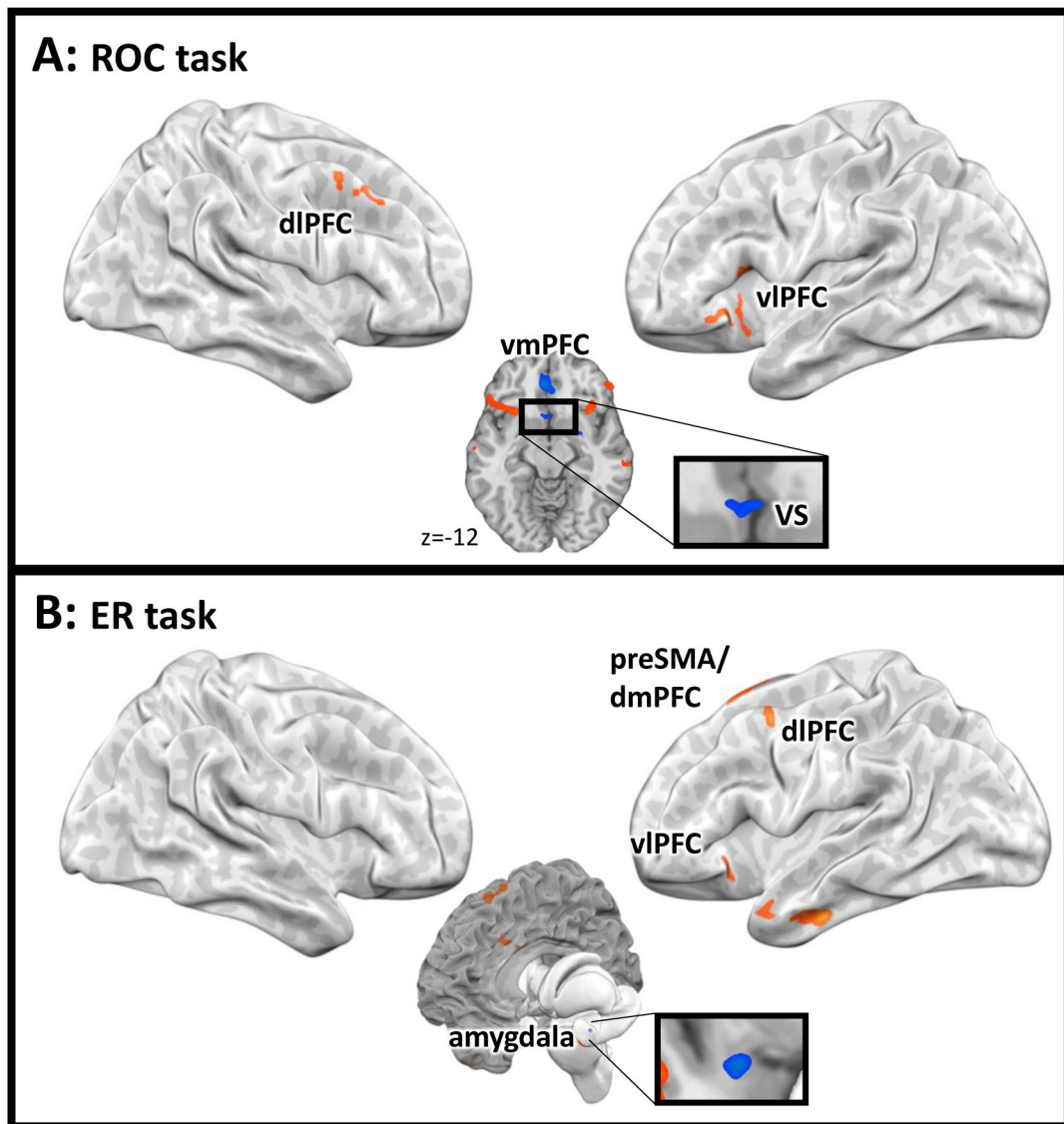


Figure 3. Regions modulated by cognitive regulation in the (A) Regulation of Craving (ROC; LATER>NOW) and (B) Emotion Regulation (ER; REAPPRAISE-Negative>LOOK-Negative) tasks. Maps are familywise-error corrected for multiple comparisons at $p < .05$ with a voxel-wise threshold of $p < .001$. Subcortical regions-of-interest (ventral striatum and ventromedial prefrontal cortex for ROC, amygdala for ER) are shown at $p < .005$, uncorrected. (*dlPFC*: dorsolateral prefrontal cortex; *vlPFC*: ventrolateral prefrontal cortex; *vmPFC*: ventromedial prefrontal cortex; *VS*: ventral striatum).

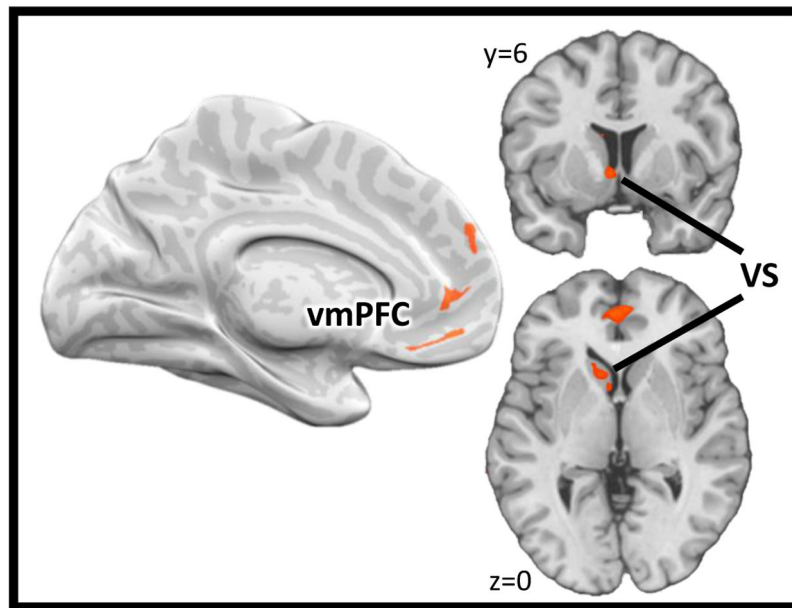


Figure 4. Regions that parametrically covaried with levels of craving in the Regulation of Craving (ROC) task trial-by-trial. Ventral striatum and ventromedial prefrontal cortex were regions-of-interest, shown uncorrected, $p < .005$. (*vmPFC*: ventromedial prefrontal cortex; *VS*: ventral striatum).

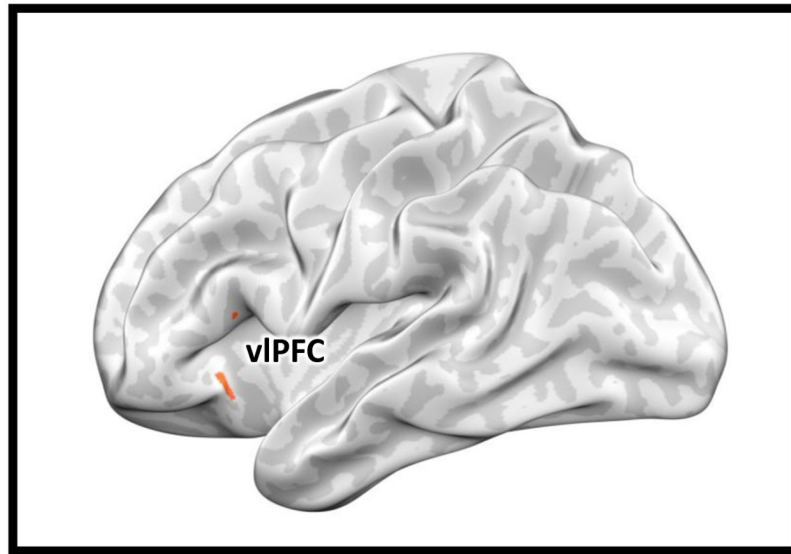


Figure 5. Regions co-activated during regulation of craving and emotion regulation (ROC LATER>NOW & ER REAPPRAISE-Negative>LOOK-Negative). Maps are familywise-error corrected for multiple comparisons at $p < .05$ with a voxel-wise threshold of $p < .001$ (*vIPFC*: ventrolateral prefrontal cortex).

Table 1.
Participant demographics for each task.

(ROC: Regulation of Craving; ER: Emotion Regulation; M: mean; SD: standard deviation; n: sample size)

Demographic Characteristics	ROC task (n=17)		ER task (n=15)	
	M/%	SD	M/%	SD
Age (in years)	33.35	10.97	32.33	9.98
Education (in years)	14.29	1.21	14.07	1.22
Gender (% Female)	41.2		40	
Ethnicity (% Hispanic)	17.6		20	
Race				
% White	47.1		40.0	
% African-American	47.1		46.7	
% More than one race	5.9		6.7	
% NA	0.0		6.7	
Diagnosis				
% Dependence	76.5		73.3	
% Abuse	23.5		26.7	
Time since Last Drink (h)	18.60	14.35	19.79	15.42
Average Drinks/Day during Past Month	8.22	5.02	7.63	4.76

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Table 2.

Peak coordinates of (A) Regions modulated by regulation of craving (ROC; LATER>NOW); **(B)** Regions modulated by negative emotion regulation (ER; REAPPRAISE-Negative>LOOK-Negative); **(C)** Region that parametrically covaried with craving during the Regulation of Craving task; **(D)** Region coactivated during regulation of both craving and negative affect; Results are $p < .05$ familywise-error corrected, with applied voxel-wise threshold of $p < .001$. (*) indicates region-of-interest small-volume familywise-error corrected at $p < .05$ with a voxel-wise threshold of $p < .005$. (A) indicates regions in the conjunction analysis that were also observed after masking with previously-identified regulation region from (78). *PFC*: Prefrontal cortex; *MNI*: Montreal Neurological Institute; *k* indicates number of 2.5mm isometric voxels; *max* indicates maximum *t* statistic in region; *mean* indicates the average *t* statistic.

Regions of Activation	Hemisphere	Peak MNI Coordinates					
		x	y	z	k	max	mean
<i>A. ROC [LATER>NOW]</i>							
Dorsolateral PFC/Middle Frontal Gyrus	Right	45	12	51	39	5.47	4.37
Ventrolateral PFC/Inferior Frontal Gyrus	Left	-42	21	-3	63	4.87	4.33
Ventral Striatum and Subgenual Anterior Cingulate*	Left	0	15	-12	6	-3.63	-3.30
Ventromedial PFC/Medial Frontal Gyrus*	Left	-3	57	-6	45	-3.18	-3.03
<i>B. ER [REAPPRAISE-Negative>LOOK-Negative]</i>							
Middle Temporal Gyrus	Left	-48	-18	-27	97	7.08	4.87
Dorsolateral PFC/Middle Frontal Gyrus	Left	-45	6	54	38	6.47	4.85
Dorsomedial PFC/Superior Frontal Gyrus	Left	-15	9	72	111	6.47	4.82
Ventrolateral PFC/Inferior Frontal Gyrus	Left	-39	21	-6	61	5.94	4.63
Amygdala*	Left	-30	3	-21	5	-4.66	-3.88
<i>C. ROC Parametric</i>							
Ventromedial PFC/Dorsomedial PFC/Medial Frontal Gyrus*	Left	3	51	3	40	5.30	3.97
Ventral Striatum*	Left	-6	6	-3	15	3.98	3.50
<i>D. Conjunction: ROC [LATER>NOW] & ER [REAPPRAISE-Negative>LOOK-Negative]</i>							
Inferior Frontal Gyrus ^A	Left	-42	21	-6	20	5.01	4.50
Inferior Frontal Gyrus	Left	-48	21	12	3	4.42	4.27